Myocardial Injury after Noncardiac Surgery: A large international prospective cohort study establishing diagnostic criteria, characteristics, predictors, and 30-day outcomes

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Study coordination: This study was coordinated by the Clinical Advances Through Research and Information Translation (CLARITY) project office in the Department of Clinical Epidemiology and Biostatistics at McMaster University and the Population Health Research Institute (PHRI), at the Hamilton Health Sciences, McMaster University, Hamilton, Ontario, Canada.

Funding sources:

Canada

1. Canadian Institutes of Health Research – 6 grants

2. Heart and Stroke Foundation of Ontario – 2 grants

3. Academic Health Science Centres Alternative Funding Plan Innovation Fund Grant

4. Population Health Research Institute Grant

5. CLARITY Research Group Grant

6. McMaster University, Department of Surgery, Surgical Associates Research Grant

7. Hamilton Health Science New Investigator Fund Grant

8. Hamilton Health Sciences Grant

9. Ontario Ministry of Resource and Innovation Grant

10. Stryker Canada

11. McMaster University, Department of Anesthesiology – 2 grants

12. Saint Joseph's Healthcare, Department of Medicine – 2 grants

13. Father Sean O'Sullivan Research Centre – 2 grants

14. McMaster University, Department of Medicine – 2 grants

15. Roche Diagnostics Global Office – 3 grants

16. Hamilton Health Sciences Summer Studentships – 6 grants

17. McMaster University, Department of Clinical Epidemiology and Biostatistics Grant

18. McMaster University, Division of Cardiology Grant

19. Canadian Network and Centre for Trials Internationally Grant

20. Winnipeg Health Sciences Foundation Operating Grant

21. University of Manitoba, Department of Surgery Research Grant – 2 grants

22. Diagnostic Services of Manitoba Research Grant – 2 grants

23. Manitoba Medical Services Foundation Grant

24. Manitoba Health Research Council Grant

25. University of Manitoba, Faculty of Dentistry Operational Fund

26. University of Manitoba, Department of Anesthesia Grant

27. University Medical Group, Department of Surgery, University of Manitoba, start-up Fund

Australia

28. National Health and Medical Research Council Program Grant

Brazil

29. Projeto Hospitais de Excelência a Serviço do SUS (PROADI-SUS) grant from the Brazilian Ministry of Health in Partnership with Hcor (Cardiac Hospital Sao Paulo-SP)

China

30. Public Policy Research Fund, Research Grant Council, Hong Kong SAR

31. General Research Fund, Research Grant Council, Hong Kong SAR

32. Australian and New Zealand College of Anesthesiologists Grant

Colombia

33. School of Nursing, Universidad Industrial de Santander

34. Grupo de Cardiología Preventiva, Universidad Autónoma de Bucaramanga

35. Fundación Cardioinfantil – Instituto de Cardiología

36. Alianza Diagnóstica S.A.

India

37. St. John's Medical College and Research Institute Grant, Division of Clinical Research and Training Grant

Malaysia

38. University of Malaya Research Grant (UMRG)

39. University of Malaya, Penyelidikan Jangka Pendek Grant (PJP)

Spain

40. Instituto de Salud Carlos III

41. Fundació La Marató de TV3

United States

42. American Heart Association Grant

United Kingdom

43. National Institute for Health Research (NIHR)

Disclosures:

The VISION Study funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation or approval of the manuscript.

Conflict of interest statement: Roche Diagnostics provided the Troponin T assays and some financial support for the VISION Study.

Running title: Myocardial Injury after Noncardiac Surgery (MINS)

ABSTRACT

Background: Myocardial injury after noncardiac surgery (MINS) was defined as prognostically relevant myocardial injury due to ischemia that occurs during or within 30 days after noncardiac surgery. Our 4 objectives were to determine the diagnostic criteria, characteristics, predictors, and 30-day outcomes of MINS.

Methods: In this international prospective cohort study of 15,065 patients aged ≥45 years who underwent in-patient noncardiac surgery, Troponin T was measured during the first 3 postoperative days. Patients with a Troponin T ≥0.04 ng/mL (elevated "abnormal" laboratory threshold) were assessed for ischemic features (i.e., ischemic symptoms and electrocardiography findings). Patients adjudicated as having a non-ischemic troponin elevation (*e.g.,* sepsis) were excluded. To establish diagnostic criteria for MINS, we used Cox regression analyses in which the dependent variable was 30-day mortality (260 deaths) and independent variables included preoperative variables, perioperative complications, and potential MINS diagnostic criteria.

Results: An elevated troponin after noncardiac surgery, irrespective of the presence of an ischemic feature, independently predicted 30-day mortality. Therefore, our diagnostic criterion for MINS was a peak Troponin T ≥0.03 ng/mL judged due to myocardial ischemia. MINS was an independent predictor of 30-day mortality (adjusted hazard ratio, 3.87; 95% CI, 2.96-5.08) and had the highest population-attributable risk (34.0%, 95% CI, 26.6-41.5) of the perioperative complications. Twelve hundred patients (8.0%) suffered MINS, and 58.2% of these patients would not have fulfilled the universal definition of myocardial infarction. Only 15.8% of MINS patients experienced an ischemic symptom.

Conclusions: Among adults undergoing noncardiac surgery, MINS is common and associated with substantial mortality.

INTRODUCTION

Worldwide, millions of patients die annually within 30 days of noncardiac surgery;[1,2] myocardial ischemia is a frequent cause.[3,4] Most noncardiac surgery studies addressing cardiac complications focus on perioperative myocardial infarction.[5-7] The "conventional" definition and diagnostic criteria of myocardial infarction in the perioperative period comes from the joint task force (European Society of Cardiology, American College of Cardiology Foundation, American Heart Association, World Heart Federation) for the universal definition of myocardial infarction.[7] This document defines myocardial infarction as myocardial necrosis in a clinical setting consistent with acute myocardial ischemia, and the most common diagnostic criteria consist of an elevated troponin value with either an ischemic symptom or an ischemic electrocardiographic finding.

Emerging evidence suggests that many patients sustain myocardial injury in the perioperative period that will not satisfy the diagnostic criteria for myocardial infarction.[8] Nevertheless, these events portend a poor prognosis that timely and appropriate intervention could potentially improve.[4] This suggests that a new diagnosis of Myocardial Injury after Noncardiac Surgery (MINS) may be useful to patients and clinicians. Our proposed definition of MINS is as follows: myocardial injury caused by ischemia (that may or may not result in necrosis), has prognostic relevance, and occurs during or within 30 days after noncardiac surgery. The definition of MINS is broader than the definition of myocardial infarction in that it not only includes myocardial infarction but also the other prognostically relevant perioperative myocardial injuries due to ischemia. MINS does not include perioperative myocardial injury that is due to a documented non-ischemic etiology (*e.g.,* pulmonary embolism, sepsis, cardioversion).

No study has established the diagnostic criteria, characteristics, predictors, and 30-day outcomes of MINS.

The Vascular events In noncardiac Surgery patIents cOhort evaluatioN (VISION) Study is a large international prospective cohort study evaluating complications after noncardiac surgery (clinicaltrials.gov, identifier NCT00512109). A prior publication of the VISION Study demonstrated that after adjustment of preoperative clinical variables (*e.g.,* age), peak Troponin T (TnT) values of 0.02 μg/L, 0.03-0.29 μg/L, and ≥0.30 μg/L in the first 3 days after noncardiac surgery were independent predictors of 30-day mortality.[3] These analyses established the prognostic relevance of troponin measurements after surgery without taking into account whether the troponin elevations were due to an ischemic or non-ischemic etiology. These analyses did not evaluate troponin elevations that occurred beyond day 3 after surgery. Finally, these analyses adjusted for only preoperative variables and did not assess for confounding through other perioperative complications. For this current publication, our primary objective was to inform the diagnostic criteria of MINS, and our secondary objectives were to determine the characteristics, predictors, and 30-day outcomes of MINS. To do this we analyzed the VISION data, evaluated troponin elevations until day 30 after surgery, excluded non-ischemic troponin elevations, and adjusted for perioperative complications.

MATERIALS AND METHODS

Study Design

We have previously described the methodology of the VISION Study.[3] This is an ongoing international prospective cohort study of a representative sample of adults undergoing noncardiac surgery. At the beginning of this study, patients had 4th generation TnT measurements after noncardiac surgery. The first 15,000 patients had event rates approximately 3 times higher than expected. Recognizing that we had sufficient events to address our objectives related to the 4th generation TnT measurements, the Operations Committee decided to subsequently monitor the 5th generation high-sensitivity TnT assay. This publication is restricted to patients enrolled during the period of 4th generation TnT use.

Patients

Eligible patients for the VISION Study had noncardiac surgery, were ≥45 years of age, received a general or regional anesthetic, and underwent elective or urgent/emergency surgery during the day or at night, during a weekday or the weekend. Patients were excluded who did not require an overnight hospital admission after surgery, who were previously enrolled in the VISION Study, or who declined informed consent. Additional exclusion criteria for the MINS study were: patients not having a 4th generation TnT measurement after surgery; patients having a TnT measurement reported as <0.04 ng/mL, <0.03 ng/mL, or <0.02 ng/mL, instead of the absolute value; patients whose troponin elevation was adjudicated as resulting from a non-ischemic etiology (*e.g.,* sepsis, pulmonary embolism, cardioversion); and patients with incomplete data for the preoperative predictors of 30-day mortality.

Research personnel primarily obtained consent prior to surgery. For those from whom

we could not obtain consent preoperatively (*e.g.,* emergency case), study personnel obtained consent within the first 24 hours after surgery. Eight centers used a deferred consent process for patients unable to provide consent (*e.g.,* patients sedated and mechanically ventilated) and for whom no next-of-kin was available.[3]

Procedures

Trained research personnel interviewed and examined patients and reviewed charts to obtain information on potential preoperative predictors of major perioperative complications using standardized definitions. Patients had blood collected to measure a Roche 4th generation Elecsys™ TnT assay 6 to 12 hours postoperatively and on the first, second, and third days after surgery. Patients enrolled between 12 and 24 hours after surgery had a TnT drawn immediately, and testing continued as indicated in the preceding sentence. All TnT measurements were analyzed at the participating hospitals, and the TnT results were reported to the attending physicians.

A TnT ≥0.04 ng/mL was the laboratory threshold considered abnormal at the time the study began. Therefore, we only obtained electrocardiography on patients who had a TnT ≥0.04 ng/mL, and we only assessed these patients for ischemic symptoms. When a patient had a TnT measurement ≥0.04 ng/mL, physicians were encouraged to obtain additional TnT measurements (to determine the peak) and electrocardiograms for several days. If a patient developed an ischemic symptom at anytime during the first 30 days after surgery, physicians were encouraged to obtain TnT measurements and electrocardiograms. We defined an ischemic feature as the presence of any ischemic symptom or ischemic electrocardiographic finding, defined in Supplemental digital content 1, Appendix 1.

Outcomes

The primary outcome was mortality at 30 days after surgery. Centers also reported the cause of death (vascular or non-vascular, definitions in Supplemental digital content 1, Appendix 2). Throughout patients' hospital stay, research personnel evaluated patients clinically, reviewed hospital charts, ensured patients had TnT measurements drawn, and documented outcome events (defined in Supplemental digital content 1, Appendix 3). We contacted patients 30 days after surgery; if patients (or next-of-kin) indicated that they had experienced an outcome, we contacted their physicians to obtain documentation.

Adjudicators evaluated all patients with an elevated troponin measurement that occurred anytime during the first 30 days after surgery to determine the presence of any ischemic features (i.e., whether a patient would have fulfilled the universal definition of myocardial infarction),[7] the presence of a non-ischemic etiology that could explain the elevated troponin measurement, and that the myocardial injury had occurred during or after surgery (i.e., no evidence to support it was due to a preoperative event). Their decisions were used in the statistical analyses.

Data Quality

At each site, an investigator reviewed and approved all data. Research personnel at participating centers submitted the case report forms and supporting documentation directly to the data management system (iDataFax™, coordinating center, McMaster University, Hamilton, Ontario, Canada). Data monitoring in VISION consisted of central data consistency checks, statistical monitoring, and on-site monitoring for all centers.[3]

Statistical Analyses

A statistical analysis plan outlining the analyses in this paper was written prior to undertaking the following analyses. For our primary objective (i.e., to establish the MINS diagnostic criteria), we undertook Cox proportional hazards models in which the dependent variable was death up to 30 days after noncardiac surgery (using a time to event analysis). In these models the independent variables were: 1. nine preoperative patient characteristics that a prior VISION analysis demonstrated were independent predictors of 30-day mortality[3] (defined in Supplemental digital content 1, Appendix 4); 2. six time-dependent perioperative adverse complications, which included the outcomes sepsis and pulmonary embolus that were not accompanied by a TnT elevation (defined in Supplemental digital content 1, Appendix 3); and 3. potential MINS diagnostic criteria. In the first model, two potential time-dependent MINS diagnostic criteria were evaluated (i.e., a peak TnT ≥0.04 ng/mL with 1 or more ischemic features and a peak TnT ≥0.04 ng/mL without an ischemic feature). The reference group was patients with a TnT ≤0.01 ng/mL. For this first model, we excluded patients with a peak TnT equal to 0.02 or 0.03 ng/mL, because a prior VISION analysis demonstrated that these thresholds were independent predictors of 30-day mortality,[3] and we did not prospectively collect data to determine whether these patients had experienced an ischemic feature (i.e., these patients did not have electrocardiography and were not assessed for ischemic symptoms).

We prespecified two potential findings that would result in different MINS diagnostic criteria. First, if both a peak TnT ≥0.04 ng/mL with and without ischemic features independently predicted mortality, then the MINS diagnostic criteria would only require a peak TnT ≥0.04 ng/mL that was judged as due to myocardial ischemia (i.e., no evidence of a non-ischemic etiology causing the TnT elevation) without requiring the presence of an ischemic feature. If this

proved the case, we planned to repeat the MINS diagnostic criteria Cox proportional hazards model, as described in the first paragraph of the statistical analysis section, including all patients and adding two more potential MINS diagnostic criteria (i.e., a peak TnT= 0.02 ng/mL and a peak TnT= 0.03 ng/mL without knowledge of whether these patients experienced an ischemic feature).

Second, if only a peak TnT ≥0.04 ng/mL with one or more ischemic features but not a peak TnT ≥0.04 ng/mL without an ischemic feature independently predicted mortality, then the MINS diagnostic criteria would require a peak TnT ≥0.04 ng/mL with an ischemic feature. This result would have prompted a repeated MINS diagnostic criteria Cox proportional hazards model with exploration of the impact of each individual ischemic feature (*e.g.,* chest pain) on 30-day mortality to determine which ischemic features should be included in the MINS diagnostic criteria.

After establishing the MINS diagnostic criteria, we determined the incidence and 95% confidence intervals (CI) of patients fulfilling these criteria. We repeated the initial Cox proportional hazards model and included MINS as a time-dependent perioperative adverse complication. For this model we determined the population-attributable risk for the independent predictors of 30-day mortality.[9,10] The population-attributable risk represents the proportion of all deaths potentially attributable to the relevant risk factor (*e.g.,* MINS). We undertook a sensitivity analysis restricted to patients in whom a preoperative estimated glomerular filtration rate (eGFR) was available, which included eGFR as a candidate independent variable.

We compared the baseline characteristics between patients who did and did not develop MINS. Across the groups proportions were compared using Fisher's exact test and continuous variables using the Student's t or Wilcoxon rank sum test, as appropriate. A Cox proportional

hazards model was undertaken to determine independent predictors of MINS up to 30 days after surgery. Potential independent variables in this model included 15 baseline clinical variables and 7 types of surgeries (defined in Supplemental digital content 1, Appendix 5). This analysis was restricted to patients in whom a preoperative eGFR was available. A sensitivity analysis omitting eGFR included all the patients.

Among patients who developed MINS, we determined the incidence of each individual ischemic feature. This analysis was restricted to patients who had a peak TnT ≥0.04 ng/mL, because patients with a peak TnT=0.03 ng/mL were not assessed for ischemic features.

We compared the cardiovascular outcomes at 30-days after surgery (defined in Supplemental digital content 1, Appendix 6) for patients who did and did not suffer MINS. For the cardiovascular outcomes, we determined the odds ratio and 95% CI. Using a Fisher's exact test, we compared the 30-day outcomes among patients who developed MINS compared to patients who did not develop MINS.

To develop a clinical risk score to predict short-term mortality among patients who suffered MINS, we conducted logistic regression analysis. The dependent variable was mortality at 30 days, and we evaluated the following candidate independent variables: preoperative variables (i.e., age, sex); and characteristics of the MINS outcome (i.e., presence of individual ischemic symptoms, presence of individual ischemic electrocardiographic findings, location of the ischemic electrocardiographic finding, and peak TnT ≥0.30 ng/mL). Our choice of candidate independent variables was based upon our hypotheses regarding which variables were likely to be most predictive and the results of prior non-operative myocardial infarction 30-day mortality risk prediction models.[11] In this logistic regression analysis, we included only patients with peak TnT ≥0.04 ng/mL, because we did not know whether patients with a peak TnT=0.03 ng/mL had

ischemic features. We further included the identified significant predictors in a separate model to determine their adjusted odds ratios. A scoring system was developed by assigning weighted points to each statistically significant predictor based on their log odds ratios, and the expected 30-day mortality risk was determined for potential risk scores using the method outlined by Sullivan et al.[12] Bootstrapping was performed to obtain 95% confidence intervals around the expected 30-day mortality risk for each potential risk score.

For all our regression models we used forced simultaneous entry (all candidate variables remained in the models regardless of statistical significance).[13,14] For patients that an adjudicator determined suffered more than one episode of MINS throughout the first 30 days after surgery, we evaluated only the first episode in all analyses. We reported adjusted odds ratios (for logistic regression) and adjusted hazard ratios (for Cox proportional hazard regression), 95% CI, and associated p-values to 3 decimal places with p-values less than 0.001 reported as $p<0.001$. For all tests, we used alpha=0.05 level of significance. In our models, we validated the odds ratios and hazard ratios and their 95% CIs through bootstrapping. For our Cox proportional hazards models, we assessed discrimination through evaluation of the C index, and we conducted sensitivity analyses in which we used frailty models to assess for center effects. For the logistic regression model, we assessed collinearity using the variance inflation factor, and we considered variables with a variance inflation factor >10 to be collinear.[15] For our logistic regression model, we assessed discrimination through evaluation of the area under the receiver operating characteristic curve, calibration with a Hosmer-Lemeshow goodness-of-fit test, and conducted sensitivity analysis in which we used a mixed model to adjust for potential clustering by center.

Our sample size was based upon our model to determine the diagnostic criteria of MINS. We evaluated 19 variables in this model and simulation studies demonstrate that regression

models require 12 events per variable evaluated.[16,17] Therefore, we required 228 deaths in our study. All analyses were performed using SAS version 9.2 (Cary, North Carolina).

Ethical Considerations and Funding Sources

The Research Ethics Board at each site approved the protocol prior to patient recruitment. Funding for this study comes from over 60 grants for VISION and its substudies.

RESULTS

Figure 1 reports the patient flow. Of the 15,065 patients included in the MINS study, 99.7% of the patients completed the 30-day follow-up. Patients were recruited at 12 centers in 8 countries in North and South America, Australia, Asia, and Europe, from August 6, 2007 to January 11, 2011.

Diagnostic Criteria of MINS (Primary Objective)

Supplemental digital content 2, Table 1 reports the results of the initial Cox proportional hazards model demonstrating that a peak TnT ≥0.04 ng/mL with and separately without an ischemic feature were independent predictors of 30-day mortality. The full model that explored all the considered diagnostic criteria for MINS demonstrated that a peak TnT ≥0.04 ng/mL with 1 or more ischemic features (adjusted hazard ratio, 4.82; 95% CI, 3.40-6.84), a peak TnT ≥0.04 ng/mL without an ischemic feature (adjusted hazard ratio, 3.30; 95% CI, 2.26-4.81), and a peak TnT=0.03 ng/mL (adjusted hazard ratio, 4.30; 95% CI, 2.68-6.91) all independently predicted 30-day mortality (Supplemental digital content 2, Table 2). Therefore after adjustment for preoperative patient characteristics and perioperative complications, a peak TnT ≥0.03 ng/mL was an independent predictor of 30-day mortality. Based on these analyses, our diagnostic criterion for MINS was any peak TnT ≥0.03 ng/mL that was judged as resulting from myocardial ischemia (i.e., no evidence of a non-ischemic etiology causing the TnT elevation).

A total of 1200 patients (8.0%; 95% CI, 7.5-8.4) fulfilled the MINS diagnostic criterion. Table 1 reports the predictors of 30-day mortality in the model that included preoperative variables and perioperative adverse complications, including MINS. Four perioperative complications (*i.e.,* MINS, sepsis, stroke, and pulmonary embolus) were independent predictors

of 30-day mortality. The independent prognostic factors identified in this model potentially explain the majority of the deaths that occurred (*i.e.,* the total population-attributable risk was 92.6%; 95% CI, 89.6-95.2); among the perioperative complications, MINS had the largest population-attributable risk (34.0%; 95% CI, 26.6-41.5). Our 30-day mortality sensitivity analysis, restricted to patients for whom a preoperative eGFR was available, demonstrated that MINS was not confounded by eGFR (i.e., MINS remained an independent predictor of 30-day mortality adjusted hazard ratio, 3.66; 95% CI, 2.71-4.93) but preoperative eGFR was not an independent predictor of 30-day mortality, p=0.480 (Supplemental digital content 2, Table 3).

Characteristics and Predictors of MINS

Supplemental digital content 3, Figure 1 depicts that 87.1% of MINS events occurred within the first 2 days after surgery. Supplemental digital content 2, Table 4 presents the baseline characteristics of patients who did and did not suffer MINS. MINS patients were older, had more cardiovascular risk factors, and known cardiovascular disease. Table 2 reports the ischemic features of patients suffering MINS of whom 84.2% (95% CI, 81.7-86.4) did not experience an ischemic symptom. A total of 34.9% (95% CI, 31.9-38.0) of MINS patients had an ischemic electrocardiographic finding, of which T wave inversion (23.3%; 95% CI, 20.7-26.1) and ST depression (16.4%; 95% CI, 14.1-18.9) were the most common. Among MINS patients 41.8% had an ischemic feature and would have fulfilled the universal definition of myocardial infarction; however, 58.2% of these patients did not experience an ischemic feature and would therefore not have fulfilled the universal definition of myocardial infarction.

We identified 12 independent predictors of MINS that included the following: age ≥75 years, cardiovascular risk factors (*e.g.,* renal insufficiency, diabetes), known cardiovascular

disease (*e.g.,* peripheral vascular disease, coronary artery disease), and surgical factors (*e.g.,* urgent/emergent surgery) (Table 3). The sensitivity analysis, which included all the patients and did not assess eGFR as a potential independent predictor of MINS, demonstrated similar findings to Table 3 except that low risk surgery was no longer predictive (adjusted hazard ratio, 0.77; 95% CI, 0.56-1.07).

Prognostic Impact of MINS

Patients with MINS were at higher risk of a nonfatal cardiac arrest (odds ratio=14.58; 95% CI, 5.75-37.02; p<0.001), congestive heart failure (odds ratio=10.34; 95% CI, 7.99-13.37; p<0.001), and stroke (odds ratio=4.66; 95% CI, 2.87-7.58; p<0.001) compared to patients who did not suffer MINS (Table 4). The 30-day mortality rate was 9.8% among patients who suffered MINS and 1.1% among patients who did not suffer MINS (OR=10.07; 95% CI, 7.84-12.94; p<0.001). Among the patients suffering MINS 115 died within 30 days of surgery, centers reported a vascular cause of death in 62 (53.9%) patients and non-vascular in 53 (46.1%). The composite of nonfatal cardiac arrest, nonfatal congestive heart failure, nonfatal stroke, and mortality occurred more frequently in patients who suffered MINS (odds ratio=9.59; 95% CI, 7.99-11.51; p<0.001). In those with and without an ischemic feature, 30-day mortality rates were 13.5% (95% CI, 10.5%-17.3%) and 7.7% (95% CI, 5.7%-10.2%), respectively.

Predictors of Mortality among Patients Suffering MINS

Age ≥75 years, ST elevation or new left bundle branch block, and anterior ischemic electrocardiographic findings were independent predictors of 30-day mortality among patients who suffered MINS (Table 5). Our scoring system to predict 30-day mortality in patients

suffering MINS assigned the following points to the independent predictor of mortality: age ≥75 years (1 point), ST elevation or new left bundle branch block (2 points), and anterior ischemic electrocardiographic findings (1 point). Figure 2 presents the expected and observed risk of 30-day mortality among the MINS patients based on the scoring system. Patients with a score of 0, 1, 2, 3, or 4 had expected 30-day mortality rates of 5.2% (95% CI, 3.3-7.4), 10.2% (95% CI, 6.5-11.9), 19.0% (95% CI, 8.7-24.3), 32.5% (95%, 10.6-45.9), and 49.8% (95% CI, 12.0-65.5), respectively.

The random effect (frailty) Cox models that adjusted for potential clustering-by-center effects produced similar results. Each variable included in the logistic regression models demonstrated a variance inflation factor <10 suggesting no collinearity. The mixed model that adjusted for any potential clustering by center in the logistic regression model produced similar results.

DISCUSSION

Principal Findings

In this international cohort study of 15,065 patients ≥45 years of age undergoing noncardiac surgery, we determined that the optimal diagnostic criterion for MINS is a peak TnT ≥0.03 ng/mL judged due to myocardial ischemia (*i.e.,* no evidence of a non-ischemic etiology causing the TnT elevation). This criterion does not require the presence of an ischemic feature. MINS was common (8.0%), associated with substantial mortality and cardiovascular complications at 30-days, and the population-attributable risk suggests that MINS explains 34.0% of the deaths that occur in adults during the first 30 days after noncardiac surgery.

A minority of MINS patients experienced an ischemic symptom; only 41.8% of MINS patients fulfilled the universal definition of myocardial infarction. Among the 58.2% of MINS patients who did not experience an ischemic feature and thus would not have fulfilled the universal definition of myocardial infarction, 1 in 13 died within 30 days.

Our Study in Relation to Other Studies

In a prior VISION publication, we demonstrated that the peak troponin measurement during the first 3 days after noncardiac surgery was an independent predictor (based on adjustment of only preoperative patient characteristics) of 30-day mortality.[3] Our current publication adds important new information by focusing on troponin elevations that were adjudicated as resulting from myocardial ischemia, evaluating all troponin elevations until day 30 after surgery, and taking into account potential confounding through risk adjustment of other perioperative complications. This is the first study to evaluate diagnostic criteria for MINS, independent predictors of MINS, and predictors of mortality in patients suffering MINS.

LeManach et al. conducted a consecutive cohort study of 1,136 patients undergoing abdominal aortic surgery in which they excluded septic patients with an elevated troponin I (Dade-Behring).[18] Consistent with our findings, they demonstrated that an elevated troponin I after surgery was an independent predictor of in-hospital mortality.[18] A limitation of this study is that they did not adjust for any perioperative complications (*e.g.,* stroke).

A multivariable analysis of data from the PeriOperative ISchemic Evaluation (POISE) Trial (an 8,351 patient international randomized controlled trial) that adjusted for preoperative factors and perioperative complications demonstrated that the highest quartile of a cardiac biomarker or enzyme elevation (i.e., a troponin or creatine kinase - myocardial band value ≥3.6 times the upper limit of normal) in patients without an ischemic feature was an independent predictor of 30-day mortality (adjusted odds ratio, 2.54; 95% CI, 1.65-3.90).[4] Although the foregoing POISE analysis supports our finding that an elevated troponin after surgery without an ischemic feature increases short-term mortality, many different troponin assays were evaluated and data were insufficient to determine prognostically relevant thresholds for the individual troponin assays.

Strengths and Limitations of Our Study

Strengths of our study included evaluation of a large contemporary representative sample of adults who underwent noncardiac surgery in 5 continents with complete follow-up data on 99.7% of the patients. All patients underwent troponin monitoring after surgery using the same troponin assay, and all patients with a TnT ≥0.04 ng/mL were prospectively assessed for ischemic symptoms and ischemic electrocardiographic findings. Our 30-day mortality model

that included MINS (based on our diagnostic criterion) demonstrated good calibration, and the results were consistent across centers.

Our study had several limitations. We systematically monitored troponin measurements only until day 3 after surgery. Therefore, after day 3, we may have missed additional MINS events in patients who did not experience an ischemic symptom. The substantial decline in MINS events by postoperative day 3 (Supplemental digital content 3, Figure 1) suggests, however, that we were not likely to have missed many MINS events. We determined the MINS diagnostic threshold only for the 4th generation TnT assay; thus, evaluation of other troponin assays will require further research.

We did not assess patients for the presence of ischemic features if their peak TnT was 0.03 ng/mL. At the start of the study we did not know that patients with a TnT of 0.03 ng/mL had an increased risk of 30-day mortality, and we assessed patients for ischemic features only if they met the laboratory threshold considered abnormal (*i.e.,* TnT ≥0.04 ng/mL). It is possible that among patients with a peak TnT=0.03 ng/mL that only those patients who also had an ischemic feature were at increased risk of 30-day mortality. Given that patients with a peak TnT ≥0.04 ng/mL did not require an ischemic feature to impact 30-day mortality, we believe it is unlikely that a peak TnT=0.03 ng/mL requires an ischemic feature to impact mortality. Our model to predict 30-day mortality in patients suffering MINS did not include patients who had a peak TnT=0.03 ng/mL. Although it is possible that our model won't predict mortality in patients with a TnT=0.03 ng/mL, this is unlikely given that a prior VISION publication did not demonstrate any difference in the risk of mortality across peak TnT values of 0.03 to 0.29 ng/mL.[3] Although experienced physicians in perioperative medicine adjudicated all elevated troponin measurements to ensure there was no evidence of a non-ischemic cause, it is possible

some non-ischemic etiologies were missed and that some events were not due to ischemic myocardial injury.

Implications

Most noncardiac surgery studies evaluating cardiac complications focus on perioperative myocardial infarction. Our results show that focusing on this complication would result in missing 58.2% of the prognostically relevant perioperative myocardial ischemic events. Based on these results and the rationale presented in our introduction, we advocate assessing surgical patients for the diagnosis of MINS. Although no randomized controlled trial has established an effective treatment for patients suffering MINS, the prognosis of these patients may be modifiable. The high-quality evidence for acetyl-salicylic acid and statin therapy in the non-operative setting,[19,20] and encouraging observational data from a large international perioperative trial (i.e., POISE) showing an association with use of these drugs and decreased 30-day mortality in patients who have suffered a perioperative myocardial injury,[4] suggests that acetyl-salicylic acid and statin therapy may benefit patients who suffer MINS.

In our study of patients ≥45 years of age undergoing noncardiac surgery, 8.0% of patients suffered MINS. It is estimated that worldwide over 100 million adults ≥45 years of age undergo major noncardiac surgery each year.[1,21] This suggests that 8 million adults may suffer MINS annually. The frequency of this perioperative complication, and the associated 30-day risk of cardiovascular complications and mortality, highlights the urgent need for clinical trials to establish strategies to prevent and treat this important complication.

A minority (15.8%) of patients suffering MINS experienced an ischemic symptom. Therefore, 84.2% of MINS probably would have gone undetected without systematic troponin

monitoring after surgery. Consistent with our finding, the third universal definition of myocardial infarction consensus statement recommends monitoring perioperative troponin measurements in high-risk patients undergoing noncardiac surgery.[7]

Conclusions

Evaluating patients for the diagnosis of MINS compared to myocardial infarction will allow physicians to avoid missing the majority of the patients who develop a prognostically relevant perioperative myocardial injury. Among adults undergoing noncardiac surgery, MINS is common (8%), and 1 in 10 patients suffering MINS will die within 30 days. Failure to monitor troponin measurements after noncardiac surgery will result in missing over 80% of MINS events.

ACKNOWLEDGEMENTS

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